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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,837	01/07/2002	Brian Dalby	INVIT1280-1	5550

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,837	DALBY ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-13,15,16,18,21-23,25-45 and 47-62* is/are pending in the application.

4a) Of the above claim(s) *2-11,18,29,30,37,42-45 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,15,16,21-23,25-28,31-36,38-41 and 51-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13,19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the "Response to Office Action" filed 5 May 2003 (Paper No. 16) in reply to the Non-Final Office Action mailed 5 November 2003 (Paper No. 12). Claims 2-11, 18, 29, 30, 37, 42-45 and 47-50 were withdrawn from consideration and claims 1, 12-17, 19-28, 31-36, 38-41 and 46 were considered in Paper No. 12. Claims 1, 14, 17, 19, 20, 24 and 46 were canceled, claims 12, 13, 21, 23, 25, 26, 28 and 32-36 were amended, and claims 51-62 were added in Paper No. 16. Claims 12, 13, 15, 16, 21-23, 25-28, 31-36, 38-41 and 51-62 are presently under consideration.

Response to Amendment

Rejection of claims 1, 14, 17, 19, 20, 24 and 46 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112

Rejection of claims 12, 13, 21-23, 25-28, 31-36 and 38-41 under 35 U.S.C. 112, first paragraph, as lacking adequate written description is withdrawn. Applicant argues persuasively that translocating polypeptides having the properties set forth in the claims were conventional in the art at the time of filing.

Rejection of claims 12, 15, 16, 21-23, 25-28, 31-36 and 38-41 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn in view of the amendments to the claims and Applicant's arguments.

Claim 13 stands rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the claimed method wherein the cell is a yeast cell for reasons of record. As pointed out in the previous Office Action, the specification is not enabling for the method wherein the plasma membrane of the cell is enclosed within a cell wall. Applicant argues that the cells of the claims no longer comprise a cell wall (page 20). However, it is known in the art that yeast cells have a cell wall (see Zinsser Microbiology, 17th Edition, Joklik *et al.* eds., Appleton-Century Crofts, New York, pages 1330-1333). Therefore, claim 13 still encompasses subject matter that is not enabled by the disclosure.

Rejection of claims 32-35 under 35 U.S.C. 112, first paragraph, as lacking enablement is withdrawn in view of the amendment of the claims such that they are no longer directed to the method wherein the cell contains a single genomic recombination site.

Claim Rejections - 35 USC § 102

Rejection of claims 12, 13, 15 and 25-27 under 35 U.S.C.§102(a) as being anticipated by Pooga *et al.* (September 1998) *Nat. Biotechnol.* 16:857-861 is withdrawn.

Rejection of claims 12, 13, 15, 16, 25, 28 and 40 under 35 U.S.C.§102(a) as anticipated by Phelan *et al.* (May 1998) *Nat. Biotechnol.* 16:440-443 is withdrawn

Rejection of claims 12 and 40 under 35 U.S.C.§102(a) as being anticipated by Phelan *et al.*(*supra*) as evidenced by Schuler and Green *Biochem. Soc. Transact.* (2001) 29:684-688 is withdrawn.

Rejection of claims 12, 13, 15 and 25-27 under 35 U.S.C.§102(b) as anticipated by Allinquant *et al.* (1995) *J. Cell Biol.*. 128:919-927 is withdrawn.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 15, 16, 21-23, 25-28, 31-36, 38-41 and 51-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*,

650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02).

The claims have been amended such that the method, which was limited to modulating expression of a target gene product in a cell in culture, now encompasses modulating expression of a target gene product in a cell wherein the cell need not be in culture. The amendment thus expands the scope of the claimed subject matter. The claims must therefore be supported by a disclosure of the method wherein the cell in which expression of a target gene product is modulated is not in culture. Applicant provides that the amendment is supported in the specification on page 2, lines 2 and 28 and on page 6, lines 14-15. However, the passages cited are not descriptions of the claimed method, but are general discussions of the properties of translocating proteins. The teachings cited do not describe a method of modulating expression of a target gene and therefore do not support the claimed method. Upon reviewing the specification, it appears that all of the teachings directed to a method of modulating expression of a target gene product in a cell specify either that the cells are in culture (e.g., page 4, paragraphs 1-3) or that the cells are transfected, which the specification defines as meaning "that a gene translocated into a cell in culture due to the translocating properties of an attached translocating polypeptides expressed in a cell" (bridging pages 7-8). Therefore, absent evidence to the contrary, the claims

as they now encompass a method for modulating expression of a target gene product in a cell not in culture constitute new matter that was not present in the application as filed.

Further, claim 35 has been amended to recite the limitation "wherein the one or more regulatory elements are flanked by site specific recombination sites". In support of the amendment, Applicant points to the passage on page 22 which states, "rather than placing a pair of recombinase sites flanking a polynucleotide segment to be excised, a single recombinase site can be incorporated". Applicant argues, "the specification states that a pair of recombination sites can be placed to flank a polynucleotide segment to be excised. Throughout the specification, the regulatory agents, which include recombinases, are stated generically to be useful for modulating target gene expression by their action on regulatory elements. Thus the specification taken as a whole described the use of recombinases to excise polynucleotide sequences (containing regulatory elements) to modulate target gene expression" (Paper No. 16, page 14). However, the passage cited by Applicant at page 22 immediately follows, and is clearly referring to, a teaching of modulating a cellular process by including a transcription blocking sequence in the regulatory element, wherein the transcription blocking sequence, not the regulatory element, is flanked by recombination sites. Although the specification teaches that regulatory elements can be modulated by excision of a piece of DNA, the only teaching to that effect is specifically directed to excision of a transcription-blocking sequence comprised within the regulatory element, and does not contemplate a regulatory element flanked by site-specific recombination sites. Thus, the method wherein the one or more regulatory elements are flanked by site-specific recombination sites constitutes new matter.

Finally, newly added claim 61 is directed to the method wherein the regulatory agent is a DNA topoisomerase. Applicant indicates that the claim is supported in the specification at page 12. However, the passage cited by Applicant teaches that the Vaccinia virus topoisomerase I protein is a preferred linker for attaching a translocating protein to a cell-modifying polynucleotide. The passage does not teach or suggest a method wherein a topoisomerase is used as a regulatory agent for the purpose of modulating expression of a target gene. Thus the claim, as it is directed to a method for modulating expression of a target gene product in a cell comprising contacting the cell with a regulatory agent attached to a translocating polypeptide, wherein the regulatory agent is a topoisomerase constitutes new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 13, 15, 16, 21-23, 25-28, 31-36, 38-41 and 51-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 21, 23 and 56 are indefinite in their recitation of "the cell in culture". There is no longer antecedent basis for the cell in culture in the amended claim. Claims 13, 15, 16, 22, 25-28, 31-36, 38-41, 51-55 and 57-62 are indefinite insofar as they depend from claim 12, 21, 23 or 56.

Claim 13 is further indefinite in being directed to the method wherein the cell is a yeast cell. As the cell of claim 12 is limited to a cell that does not have a cell wall, the yeast cell falls

outside of the subject matter encompassed by claim 12. Therefore, there is no antecedent basis for the yeast cell in the base claim.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 56 and 57 are rejected under 35 U.S.C.§102(a) as being anticipated by Phelan *et al.* (May 1998) *Nat. Biotechnol.* 16:440-443, as applied to claim 1 in Paper No. 12, and as evidenced by the NiceProt View of Swiss-Prot: P04637 (available at http://us.expasy.org).

Phelan *et al.* teach a method for modulating apoptosis comprising, contacting a cell in culture under suitable conditions with a cell process-modifying p53 molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule (i.e. p53 regulatory elements), thereby modulating expression of p53 responsive genes in the cell in culture (see especially page 442 and Figures 3 and 5 and the captions thereto). The NiceProt View of Swiss-Prot: P04637 teaches that p53 is a DNA-binding protein. Therefore, the method of Phelan *et al.* anticipates claims 56 and 57.

Claims 56 and 57 are rejected under 35 U.S.C.§102(e) as being anticipated by O'Hare *et al.* U.S. Patent No. 6,017,735 (made of record in the IDS filed 14 May 2003), as evidenced by the NiceProt View of Swiss-Prot: P04637 (available at http://us.expasy.org).

O'Hare *et al.* teach a method for modulating apoptosis comprising, contacting a cell in culture under suitable conditions with a cell process-modifying p53 molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule (i.e., p53 regulatory elements), thereby modulating expression of p53 responsive genes in the cell in culture (see especially column 16, paragraphs 4-7). The NiceProt View of Swiss-Prot: P04637 teaches that p53 is a DNA-binding protein. Therefore, the method of Phelan *et al.* anticipates claims 56 and 57.

Conclusion

Applicant's amendment and submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 14 May 2003 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
July 21, 2003

JAMES KETTER
PRIMARY EXAMINER